PATENT COOPERATION TREATY

From the
INTERNATIONAL SEARCHING AUTHORITY

To:
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PCT

WRITTEN OPINION OF THE INTERNATIONAL SEARCHING AUTHORITY

(PCT Rule 43*bis*.1)

Date of mailing (*day/month/year*)	16 JUN 2006
Applicant's or agent's file reference 213.1204-PCT	FOR FURTHER ACTION See paragraph 2 below

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US05/06575	28 February 2005 (28.02.2005)	01 March 2004 (01.03.2004)

International Patent Classification (IPC) or both national classification and IPC

IPC: A61K 38/21(2006.01)
USPC: 424/85.6

Applicant

ENZON PHARMACEUTICALS, INC.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I — Basis of the opinion
- ☐ Box No. II — Priority
- ☐ Box No. III — Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV — Lack of unity of invention
- ☒ Box No. V — Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI — Certain documents cited
- ☐ Box No. VII — Certain defects in the international application
- ☐ Box No. VIII — Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA") except that this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1*bis*(*b*) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of 3 months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA/ US	Date of completion of this opinion	Authorized officer
Mail Stop PCT, Attn: ISA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (571) 273-3201	31 May 2006 (31.05.2006)	Gary Nickol, Ph.D. Telephone No. (571) 272-0600

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Box No. I Basis of this opinion

1. With regard to the language, this opinion has been established on the basis of:

☒ the international application in the language in which it was filed

☐ a translation of the international application into _____, which is the language of a translation furnished for the purposes of international search (Rules 12.3(a) and 23.1(b)).

2. With regard to any nucleotide and/or amino acid sequence disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:

a. type of material

☐ a sequence listing

☐ table(s) related to the sequence listing

b. format of material

☐ on paper

☐ in electronic form

c. time of filing/furnishing

☐ contained in the international application as filed.

☐ filed together with the international application in electronic form.

☐ furnished subsequently to this Authority for the purposes of search.

3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

4. Additional comments:

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Box No. V Reasoned statement under Rule 43 *bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims 4-6, 9-10, 17-32, 40-46, 48-54	YES
	Claims 1-3, 7-8, 11-16, 33-39, 47	NO
Inventive step (IS)	Claims NONE	YES
	Claims 1-54	NO
Industrial applicability (IA)	Claims 1-54	YES
	Claims NONE	NO

2. Citations and explanations:

Please See Continuation Sheet

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

V. 2. Citations and Explanations:

Claims 1-3, 7-8, 11-16, and 47 lack novelty under PCT Article 33(2) as being anticipated by Pedersen *et al*. The claims of the instant invention are drawn to a composition comprising an interferon conjugated to a polyalkylene oxide polymer and further comprising other excipients, methods of making said conjugated interferon, and methods of treating a mammal with said interferon-polymer conjugate. Pedersen *et al* teaches interferon (IFN)-β molecules conjugated to various types of polymers, including polyethylene glycol (PEG). Pedersen *et al* also teaches pharmaceutical compositions of the conjugated IFN-β molecules comprising excipients such as sodium acetate, mannitol, glycine, trehalose, sucrose, glycerol, and polysorbate-20 and -80. Pedersen *et al* also discloses methods of treating patients with the said conjugated IFN-β compositions.

Claims 1-3, 7-8, 11-16, 33-39, and 47 lack novelty under PCT Article 33(2) as being anticipated by Drustrup. The claims of the instant invention are drawn to a composition comprising an interferon conjugated to a polyalkylene oxide polymer and further comprising other excipients, methods of making said conjugated interferon, and methods of treating a mammal with said interferon-polymer conjugate. Drustrup teaches IFN-β molecules conjugated to PEG, methods of specifically pegylating IFN-β molecules, and pharmaceutical compositions of the IFN-β-PEG conjugates further comprising excipients such as mannitol, glycine, sodium acetate, trehalose, sucrose, glycerol, and polysorbate-20 and -80. Drustrup also teaches methods of administering said compositions for treatment of patients in need.

Claims 4-6, 9-10, 17-46, and 49-54 lack an inventive step under PCT Article 33(3) as being obvious over Pedersen *et al*. The subject matter and the teachings of Pedersen *et* al are described above. The claims of the instant application are further drawn to compositions with specific pH ranges and buffer concentrations, and polymers with specific weights. The claims are also drawn to specific polymers for conjugation, and specific methods of conjugating IFN-β molecules with polymers. Pedersen *et al* is silent regarding compositions with the claimed pH ranges and buffer concentrations. However, it would be obvious to one of ordinary skill in the art to optimize any pharmaceutical composition with respect to pH and buffer concentration. Such optimization is routine and common in the art. Pedersen *et al* also is silent regarding any specific branched polymers and methods of conjugating said polymers to IFN-β. However, many types of PEG polymers are known in the art, as well as methods of conjugating PEG polymers to specific amino acids, including lysine. A person of ordinary skill in the art would be familiar with different types of PEG polymers, and would also be familiar with the chemistry and methods of attaching such polymers. Therefore, one of ordinary skill in the art would also have the motivation and a reasonable expectation of success in creating IFN-β molecules conjugated to various branched PEG polymers.

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Supplemental Box
In case the space in any of the preceding boxes is not sufficient.

Claims 4-6, 9-10, 17-32, 40-46, and 48-54 lack an inventive step under PCT Article 33(3) as being obvious over Drustrup. The subject matter and the teachings of Drustrup are described above. The claims of the instant application are further drawn to compositions with specific pH ranges and buffer concentrations, and polymers with specific weights. The claims are also drawn to specific polymers for conjugation, and specific methods of conjugating IFN-β molecules with polymers. Drustrup is silent regarding compositions with the claimed pH ranges and buffer concentrations. However, it would be obvious to one of ordinary skill in the art to optimize any pharmaceutical composition with respect to pH and buffer concentration. Such optimization is routine and common in the art. Drustrup also is silent regarding any specific branched polymers. However, many types of PEG polymers are known in the art, as well as methods of conjugating PEG polymers to specific amino acids, including lysine. A person of ordinary skill in the art would be familiar with different types of PEG polymers. Therefore, one of ordinary skill in the art would also have the motivation and a reasonable expectation of success in creating IFN-β molecules conjugated to various branched PEG polymers.

Claims 1-54 meet the criteria set out in PCT Article 33(4), and thus possess industrial applicability because the subject matter claimed can be made or used in industry.

Please See Continuation Sheet

Claims 4-6, 9-10, 17-32, 40-46, and 48-54 meet the criteria set out in PCT Article 33(2), because the prior art does not teach or fairly suggest an IFN-b composition comprising IFN-b conjugated to a polyalkylene oxide polymer and further comprising the claimed excipients, methods of making said conjugated IFN-b, and methods of treating a mammal with said IFN-polymer conjugate.